# Sleep Apnea and Cardiovascular Disease
## An Enigmatic Risk Factor

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***Abstract:*** **Synchronization of molecular, metabolic, and cardiovascular circadian oscillations is fundamental to human health. Sleep-disordered breathing, which disrupts such temporal congruence, elicits hemodynamic, autonomic, chemical, and inflammatory disturbances with acute and long-term consequences for heart, brain, and circulatory and metabolic function. Sleep apnea afflicts a substantial proportion of adult men and women but is more prevalent in those with established cardiovascular diseases and especially fluid-retaining states. Despite the experimental, epidemiological, observational, and interventional evidence assembled in support of these concepts, this substantial body of work has had relatively modest pragmatic impact, thus far, on the discipline of cardiology. Contemporary estimates of cardiovascular risk still are derived typically from data acquired during wakefulness. The impact of sleep-related breathing disorders rarely is entered into such calculations or integrated into diagnostic disease-specific algorithms or therapeutic recommendations. Reasons for this include absence of apnea-related symptoms in most with cardiovascular disease, impediments to efficient diagnosis at the population level, debate as to target, suboptimal therapies, difficulties mounting large randomized trials of sleep-specific interventions, and the challenging results of those few prospective cardiovascular outcome trials that have been completed and reported. The objectives of this review are to delineate the bidirectional interrelationship between sleep-disordered breathing and cardiovascular disease, consider the findings and implications of observational and randomized trials of treatment, frame the current state of clinical equipoise, identify principal current controversies and potential paths to their resolution, and anticipate future directions.** **(*Circ Res*. 2018;122:1741-1764. DOI: 10.1161/CIRCRESAHA.118.310783.)**

**Key Words:** cardiovascular risk factors ■ heart failure ■ humans ■ sleep apnea, central ■ sleep apnea, obstructive



Blood pressure (BP), heart rate, and sympathetic nervous system activity naturally fall with nonrapid eye movement sleep and then elevate on wakening.[1] This cardiovascular circadian rhythm is but one external expression of a corporeal molecular–metabolic synchrony evolved to advantage a species more active during light than darkness.

Cardiac metabolic gene expression displays a norepinephrine (NE)-sensitive circadian rhythm, coordinating substrate availability with anticipated changes in myocardial workload. In experimental preparations, temporal misalignment of such gene expression with myocardial metabolic demand promotes left ventricular (LV) hypertrophy, insulin resistance, and reperfusion injury,[2,3] and in a model of myocardial infarction, maladaptive cardiac remodeling, involving impaired early innate immune, repair, and angiogenic responses.[4] Similar challenge to molecular oscillators in vascular endothelium, smooth muscle, and fibroblasts alters normal circadian variation in α-adrenoceptor responsiveness, NO synthesis and bioavailability, and propensity to thrombosis.[3,5]

Volitional disruption of such molecular–autonomic–hemodynamic rhythms, as occurs with regular shift work, predisposes to metabolic morbidities, hypertension, and myocardial infarction. An intrinsically short sleep duration or its involuntary interruption, foreshortening, or restriction alters normal glucose metabolism and increases the likelihood of developing hypertension, type II diabetes mellitus, obesity, coronary heart disease, stroke, and premature death.[6,7] However, the most vigorous challenge to the normal nocturnal confluence of circadian molecular, metabolic, autonomic, and hemodynamic rhythms is interruption of sleep by unremitting cycles of apnea and arousal.

The initial clinical impetus to identify and treat sleep apnea (SA) was to alleviate excessive daytime sleepiness (EDS). Cardiologists became engaged after the detection, in patients with cardiovascular conditions, of a disproportionately high prevalence of asymptomatic SA relative to the general population (Table 1); the emergence of physiological, epidemiological, and observational data linking sleep-related breathing disorders to cardiovascular risk factors, events, and premature mortality; and the revelation that SA-specific treatment might offer a novel, nonpharmacological means of maintaining, stabilizing, or restoring cardiovascular health.[8] Still, contemporary cardiovascular risk estimates and therapeutic algorithms consider only data acquired during wakefulness. The impact of sleep-related breathing disorders on risk or the potential mitigation of such risk with treatment is rarely integrated into

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**Nonstandard Abbreviations and Acronyms**

| | |
|---|---|
| ADVENT-HF | Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure |
| AHI | apnea–hypopnea index |
| ASV | adaptive servo ventilation |
| BMI | body mass index |
| BNP | B-type natriuretic peptide |
| BP | blood pressure |
| CANPAP | Canadian Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure |
| CAT-HF | Cardiovascular Improvements With MV-ASV Therapy in Heart Failure |
| CI | confidence intervals |
| CPAP | continuous positive airway pressure |
| CSA | central sleep apnea |
| CSR | Cheyne–Stokes respiration |
| EDS | excessive daytime sleepiness |
| ESS | Epworth sleepiness scale |
| HbA1c | hemoglobin A1c |
| HF | heart failure |
| HFrEF | heart failure with reduced ejection fraction |
| HR | hazard ratio |
| LV | left ventricle |
| LVEF | left ventricular ejection fraction |
| MSNA | muscle sympathetic nerve activity |
| mv-ASV | minute ventilation-triggered ASV |
| NF | nuclear factor |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| OR | odds ratio |
| OSA | obstructive sleep apnea |
| PAI-1 | plasminogen activator inhibitor-1 |
| PAP | positive airway pressure |
| REM | rapid eye movement |
| SA | sleep apnea |
| SAVE | Sleep Apnea Cardiovascular Endpoints |
| SDB | sleep-disordered breathing |
| SERVE-HF | Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure |
| SHHS | Sleep Heart Health Study |
| $TST_{90}$ | total sleep time with oxygen saturation <90% |
| WSC | Wisconsin Sleep Cohort |

such calculations. The present work focuses on the cardiovascular consequences of SA and its specific therapy.

## SA Pathophysiology and Prevalence

Obstructive hypopnea or apnea occurs when the upper airway narrows or closes completely during sleep. Pharyngeal occlusion triggers an immediate sequence of pathological disturbances with adverse implications for the heart and vasculature.[9] First is an abrupt drop in intrathoracic pressure, by as much as −60 mm Hg.[10] This event increases transmural pressure across all cardiac chambers and great vessels and is a potentially reversible cause of thoracic aortic dilatation or dissection (Table 2).[11,12] Lower pulmonary vasculature impedance increased systemic venous return; ventricular interaction can reduce left-sided preload.[13] The acute increase in LV wall stress does not diminish normal systolic function, but if this is impaired, stroke volume falls and sympathetic nerve firing increases reflexively.[14]

By silencing inhibitory input from pulmonary stretch receptors converging on brain stem adrenergic centers, cessation of breathing will increase efferent sympathetic vasoconstrictor discharge.[9] With continued apnea, arterial oxygen desaturation and a gradual rise in $PaCO_2$ stimulate chemoreceptors, eliciting reflex-mediated sympathetic excitation and neural NE release.[9] Engagement of renal nerves can elicit an acute, profound reduction in kidney blood flow.[15] Hypoxia also increases reflexively efferent vagal tone.[9] Acutely, the adverse mechanical–autonomic interactions, elicited by each obstructive event, can trigger atrial and ventricular arrhythmias.[16–18] Chronic exposure to intermittent hypoxia can deplete carotid bodies of NO,[19] potentiate peripheral chemoreceptor reflex sensitivity,[20] and increase pulmonary vascular resistance.[13,21]

Apnea terminates after 30 to 90 seconds with an arousal—a central neural event that reduces parasympathetic sinoatrial input and concurrently stimulates sympathetic outflow even further.[9] Often, the resulting cumulative BP surge can exceed average waking values.[22] Resumption of breathing normalizes blood chemistry, but the acute inflammatory stress induced by the generation of reactive oxygen species can, in time, impair vascular endothelial function and increase aortic stiffness.[23–25]

One measure of SA severity, derived from polysomnographic recordings, is the apnea–hypopnea index (AHI). This ratio represents the average hourly frequency of apnea (airflow absent for >10 seconds) plus hypopnea (airflow diminution associated with a fall in arterial oxyhemoglobin saturation of ≥3% or terminated by an electroencephalographic arousal) during sleep. Apneas and hypopneas are classified as obstructive if accompanied by inspiratory effort against the occluded pharynx or signs of upper airway flow limitation, respectively, and as central if these signs are absent.[26] Between 0 and 5 events per hour is considered normal; from 5 to 15 events per

**Table 1. Prevalence of Obstructive Sleep Apnea in Populations With Cardiovascular Disorders**

| Condition | % |
|---|---|
| Hypertension | 30–83 |
| Ischemic heart disease | 30–58 |
| Stroke | 43–91 |
| HF, with reduced ejection fraction | 12–53 |
| HF, with preserved ejection fraction | 40 |
| Hypertrophic cardiomyopathy | 40 |
| Atrial fibrillation | 25–80 |
| End-stage renal disease | 40–60 |

HF indicates heart failure.

**Table 2. Obstructive Apnea: Negative Intrathoracic Pressure**

| |
|---|
| A cardiac afterload unique to OSA |
| Not detected by brachial BP measurement |
| Not affected by antihypertensive therapy |
| Acute: ↑ atrial, ventricular, and thoracic aorta wall tension, myocardial $O_2$ demand; ↓ coronary blood flow; if HFrEF: ↓ stroke volume, reflexive ↑ in sympathetic nerve firing and NE release |
| Chronic: ↑ risk of atrial fibrillation, atrial and ventricular hypertrophy or dilatation, thoracic aortic dilatation |

BP indicates blood pressure; HFrEF, heart failure with reduced ejection fraction; NE, norepinephrine; and OSA, obstructive sleep apnea.

hour, mild; between 15 and 30 events per hour, moderate; and >30 events per hour, severe SA.[26]

The prevalence of obstructive SA (OSA) has increased over time, in parallel with average body mass index (BMI).[27] Of those now aged between 30 and 70 years, OSA with an AHI ≥5 events per hour is estimated to afflict ≈34% of men and 17% of women and an obstructive AHI ≥15 ≈14% and 7%, respectively.[27] A recent Swiss population survey, applying more liberal scoring criteria for hypopnea,[26] ascertained an AHI ≥15 in 23% of women and 50% of men aged 35 to 75 years; this sex difference narrowed after menopause.[28] The AHI can vary considerably from night to night because of changes in alcohol or sodium consumption or in the volume of fluid that redistributes overnight from the legs to the neck, where is promotes upper airway narrowing or collapse.[8,29] Importantly, in individuals with coexisting cardiovascular conditions, the prevalence of asymptomatic OSA is higher and independent of BMI than in otherwise healthy adults of similar age and sex.[8,30] Consequently, if it is assumed that sleepiness or obesity are axiomatic to the OSA phenotype, its prevalence among patients with cardiovascular disease will be underestimated.[27,28,31]

In contrast, the ventilatory instability characteristic of central SA (CSA) seldom arises in healthy adults[32] but can be detected at a frequency of ≥15 events per hour in up to one third of patients with atrial fibrillation and normal ventricular systolic function[33] or with heart failure (HF), regardless of ejection fraction.[33–35] CSA initiates if hyperventilation, stimulated reflexively by pulmonary receptors sensitive to congestion, reduces $PaCO_2$ below the apneic threshold (which rises with sleep), resulting in complete or partial (ie, hypopnea) withdrawal of the respiratory drive to breathe.[36] Apnea and oxygen desaturation increase muscle sympathetic nerve activity (MSNA) reflexively.[37] CSA, with its archetypical cycles of waxing and waning tidal volume, termed Cheyne–Stokes respiration (CSR), presents far more commonly in men than in women.[38–41] The principal cause of paroxysmal nocturnal dyspnea, CSR can develop also in patients with OSA and HF with reduced ejection fraction (HFrEF) if lung-to-ear circulation time is prolonged.[42,43]

OSA and CSA interrupt breathing by different mechanisms yet impose qualitatively similar autonomic, chemical, mechanical, and inflammatory burdens on the heart and circulation. The principal quantitative differences between these 2 apnea forms are the more negative intrathoracic pressure (and hence greater LV and atrial afterload) induced by obstructive events and the lower average awake $PaCO_2$ and generally greater sympathoexcitation in the latter.[41,44] One apnea type generally predominates but during the course of a single night arterial $Pco_2$ can fall and OSA transition to CSA if incessant surges in afterload induced by airway collapse further impair ventricular systolic performance. Over time, OSA can transform into a pattern of predominantly CSA; if ventricular filling pressures improve with treatment, CSA can revert to OSA.[45]

## Cardiovascular risk

Each apneic episode ordinarily lasts a minute or less but when repeated hour by hour, night after night, for years or decades, the hemodynamic, autonomic, chemical, and inflammatory disturbances elicited can exert long-term aftereffects on the heart, brain, circulation, and metabolism. Thus, apneas can trigger events during sleep, and cardiovascular events can accrue long after apneas cease on awakening.

Mismatch between myocardial oxygen delivery during apnea and the metabolic requirements imposed by acute increases in intrathoracic and systemic arterial pressure render the heart vulnerable to nocturnal ischemia, myocardial infarction, and ventricular arrhythmias.[9,46,47] Individuals with OSA have a temporally distinct circadian distribution of sudden cardiac death, with a 2-fold increase in occurrence between midnight and 6 AM.[48] In a subsequent large longitudinal study, indices of nocturnal hypoxemia were the strongest predictors of sudden death risk, with hazard ratios (HRs) between 2.6 and 2.93.[49]

Intrathoracic structures may remodel in response to the cyclic imposition of negative pressure, resulting in atrial dilatation and fibrosis, increasing susceptibility to fibrillation,[18,50] BP-independent LV[51] or focal basal septal hypertrophy,[52] thoracic aortic dilatation,[11,12] or impaired recovery of right or LV function after myocardial infarction.[53,54]

The sustained aftereffects of recurrent obstructive apneas during sleep include ignition of inflammatory systems. Inflammation impairs endothelial-mediated vasodilatation, stiffens conduit arteries, and promotes or accelerates carotid atherosclerosis, coronary artery calcification, and acute coronary syndromes.[23–25,55–57] In a comparative analysis of 4 cohorts having either severe OSA, hypertension, both, or neither, the only variable associated independently with LV mass index was increased pulse wave velocity, a sign of greater conduit arterial stiffness.[51]

Importantly, apnea-induced sympathetic excitation does not subside with waking. Sleep disruption and OSA induce an autonomic neuroplasticity resulting in sustained elevation of the central set point for muscle sympathetic nerve firing during wakefulness.[58–60] Sensitization of the carotid body by recurrent hypoxia will amplify further the magnitude of sympathetic outflow.[20,59] Chronic activation of the sympathetic nervous system underlies the pathophysiology of a range of cardiometabolic disorders; its magnitude predicts cardiovascular morbidity, foreshortened lifespan, and sudden cardiac death.[16,61,62] Concordant increases in efferent renal sympathetic nerve traffic stimulate both noradrenergic and renin–aldosterone–mediated sodium and water retention. With rostral fluid shift of retained fluid exacerbating OSA or CSA and apnea further amplifying neurohumoral sympathetic excitation, this bidirectional physiology contributes importantly to the high prevalence of SA in sodium-retaining states, including HF, hypertension, and end-stage renal disease.[8,63] Thus, OSA may precede, induce, exacerbate, or result from these conditions.[8]

The intensity of skeletal muscle sympathetic nerve discharge in the awake state is directly proportional to both the AHI and the frequency of nocturnal arousals and relates inversely to the oxygen desaturation index.[31] Magnetic resonance imaging, focusing on elements of the cortical autonomic network, has revealed desaturation-related thinning of the left posterior cingulate cortex and dorsal posterior insular cortices bilaterally; thickening of the left midcingulate cortex and bilateral thalami in individuals with moderate-to-severe OSA; and a significant positive relationship between thickening of these regions and MSNA[60] (Figure 1). Chronically

elevated input from peripheral chemoreceptors sensitized by recurrent nocturnal hypoxemia is one plausible mechanism for such thickening.[20,59]

As anticipated by such pathophysiology, community-based epidemiological and observational studies and long-term follow-up of selected cohorts document a positive relationship between the severity of SA and the development of cardiometabolic disorders, the frequency of cardiovascular events, and death rates.[8] At the 18-year follow-up of the WSC study (Wisconsin Sleep Cohort) of 1522 population-based subjects assessed at recruitment with polysomnography, the adjusted HR for all-cause mortality for those with an untreated AHI ≥30 was 3.8 (95% confidence intervals [CIs], 1.6–9.0); adjusted HR for cardiovascular mortality was 5.2 (CI, 1.4–19.2).[64]

The SHHS (Sleep Heart Health Study) recruited a multiethnic cohort of 6441 adults aged >40 years from existing American population-based studies of cardiovascular and pulmonary disease. AHI was derived between 1995 and 1998 using in-home polysomnography. After a mean 8.2-year follow-up, the adjusted HR for all-cause mortality if AHI was ≥30 versus <5 was 1.46 (CI, 1.14–1.86)[65] (Figure 2). Male mortality rates exceeded those of females; in analyses stratified by sex and age, AHI associated with mortality only in men under the age of 70 years. The percentage of total sleep time with oxyhemoglobin saturation <90% ($TST_{90}$) was independently associated with all-cause mortality. In men with an AHI ≥15, the adjusted HR for cardiovascular mortality when compared with an AHI <5 was 1.69 (CI, 1.13–2.52); no corresponding increase in risk was observed in women.[65]

Spanish investigators have published several reports concerning the fate of individuals characterized by polysomnography. In a series of men referred for polysomnography and followed for on average 10 years, the cumulative incidence of fatal and nonfatal cardiovascular events was 3.5- and 4.7-fold higher, respectively, in those with severe untreated OSA than in healthy individuals, but in those treated with continuous positive airway pressure (CPAP), event rates tracked those of snoring or healthy reference subjects.[66] For women, cardiovascular mortality rates averaged 3.71 per 100 patient years in those with an untreated AHI ≥30 but 0.31 if treated with CPAP and 0.28 if AHI was <10.[67] Both an observational study of men and women aged ≥65 years and that of a Dutch cohort reported heightened risk without treatment but its mitigation if CPAP was prescribed.[68,69] In a retrospective multivariable analysis of a Canadian cohort (10 149 adults referred for diagnostic polysomnography) controlling for conventional cardiovascular risk factors, only $TST_{90}$ was a significant independent predictor, after a median follow-up of 68 months, of a composite end point incorporating cardiovascular events and all-cause mortality (adjusted HR, 1.50; CI, 1.25–1.79), whereas the AHI did not associate significantly with event-free survival.[70]

## Hypertension

Each of the sympathoexcitatory, inflammatory, neurohumoral, and mechanical consequences of OSA is a potential stimulus to hypertension or ventricular hypertrophy. OSA and hypertension frequently coexist; OSA is detected more often when primary hypertension is present and hypertension is diagnosed more often in individuals with than without OSA.[1,71,72] This overlap may represent the presence of shared pathophysiological disturbances, elevating vascular resistance and inducing sodium and water retention.[73,74]

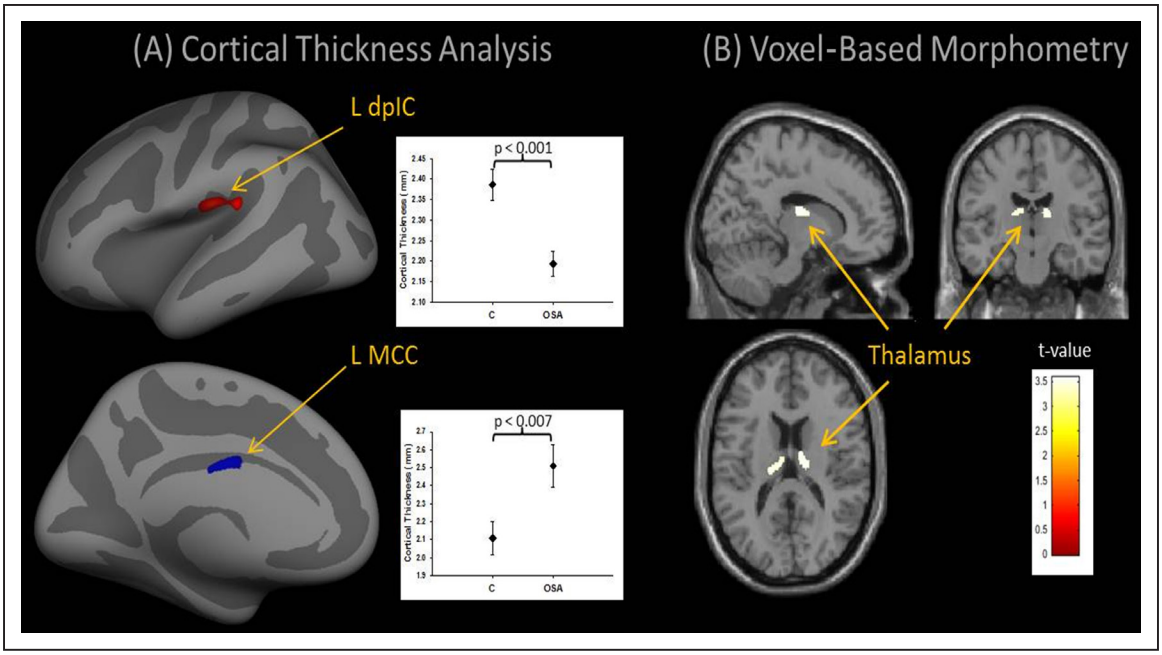


**Figure 1. Group mean gray matter differences in key cortical autonomic regions between individuals with and without obstructive sleep apnea (OSA).** Cortical thickness (**A**) and voxel-based morphometric (**B**) analysis of 19 sex- and age-matched control (**C**) participants with no or mild OSA and 22 with moderate-to-severe OSA demonstrates, in the latter, significant thinning of the left dorsal posterior insular cortex (L dpIC) and thickening of the left midcingulate cortex (L MCC). L dpIC thinning correlated inversely with participants' oxygen desaturation index; L MCC thickness correlated directly with muscle sympathetic burst incidence recorded with participants awake and resting supine ($r$=0.46; $P$=0.002). Reprinted from Taylor et al[60] with permission. Copyright ©2017, Oxford University Press.

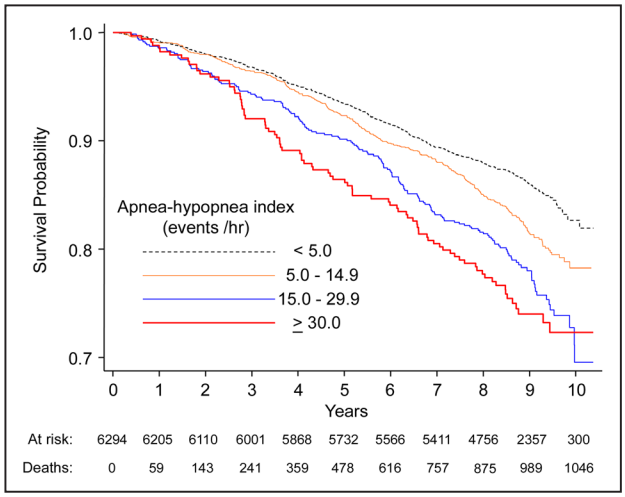


**Figure 2. Sleep Heart Health Study cohort.** Kaplan–Meier survival curves categorized by baseline apnea–hypopnea index. Reprinted from Punjabi et al[65] with permission. Copyright ©2009, Punjabi et al.

Primary hypertension is, in general, characterized by increased efferent cardiac, renal, and muscle sympathetic activity.[62] Heightened daytime sympathetic nerve firing rates or plasma NE concentrations in those with OSA cannot be attributed to obesity and do not associate consistently with elevated systemic arterial pressure,[31,75] indicating considerable between-subject variance in neurovascular transduction.

In prospective population surveys, the prevalence of hypertension in individuals with an AHI >15 events per hour has ranged between 13% and 60%,[71,72] with adjusted odds ratios (ORs) for elevated BP highest in those under the age of 60 years.[72] In 3670 SHHS participants not prescribed antihypertensive therapy, there was, after adjustment, a linear relationship between BP and both the AHI and the arousal index.[76] OSA severity, whether judged by the AHI or the magnitude of desaturation, increased the OR for prevalent hypertension.[76] By contrast, in a subsequent observational study, the prevalence of hypertension was a function of the arousal index (a predictor of increased daytime MSNA[31]), rather than the AHI or the magnitude of oxygen desaturation.[77] The HypnoLaus population survey calculated a fully adjusted OR for hypertension prevalence of 1.6 (95% CI, 1.14–2.26) for an AHI >20.[28] A recent meta-analysis of 6 trials found men but not women with OSA at risk of prevalent hypertension.[78]

Notably, these particular studies evaluated only daytime BP. When sleep is disrupted by OSA, the typical BP dip from average awake values is attenuated and in some even reversed.[79,80] The proportion of both men and women with nondipping BP during sleep is significantly higher if OSA is present[80]; in hypertensive individuals, the likelihood of an attenuated systolic BP fall during sleep increases in parallel with the AHI.[81] Importantly, average nighttime BP, a rise in BP with sleep, and visit-to-visit BP variability outperform average clinic or daytime ambulatory readings as predictors of target organ damage or fatal or nonfatal cardiovascular events.[82–84]

Now considered the most common secondary cause of hypertension,[85] OSA has been detected in ≤90% of patients with drug-resistant hypertension, often accompanied by mineralocorticoid excess.[86] In a consecutive series of 71 such patients, plasma aldosterone concentration correlated significantly with the AHI.[86] In addition to stimulating oxidative stress, inflammation, ventricular hypertrophy, and fibrosis,[87] hyperaldosteronism can render OSA more severe by promoting sodium retention and nighttime rostral fluid shift into peripharyngeal tissue.[8]

In a canine model of reversible OSA, sustained daytime hypertension was induced by 1 to 3 months of intermittent airway occlusion during sleep but not by recurrent arousal without obstruction.[88] However, in humans, evidence for a causal relationship is less clear-cut. In the prospective WSC study, a significant linear dose–response relationship between baseline AHI and the development of hypertension emerged after 4 years. For an AHI ≥15, the OR, when adjusted for baseline hypertension, age, sex, BMI, and other factors, was 2.89 (CI, 1.46–5.64).[71] However, the SHHS investigators were unable to replicate this observation if data were adjusted for baseline BMI.[89]

In meta-analyses of randomized controlled trials, the impact of treating OSA has been modest, averaging ≈2/2 mm Hg, regardless of whether CPAP or mandibular advancement devices were studied.[90] A meta-analysis specific to positive airway pressure (PAP) reported weighted mean differences of −2.58/−2.01 mm Hg for diurnal BP and −4.09/−1.85 mm Hg for nocturnal BP.[91] Younger age, higher Epworth sleepiness scale (ESS), more severe OSA, and greater adherence to PAP all predicted responsiveness,[91] with each hour of nightly CPAP use achieving an additional 1.5/0.9 mm Hg reduction.[90] Ironically, in a controlled intervention trial, avoidance of sleeping supine achieved substantially greater reductions in average daytime and nighttime ambulatory BP.[92] Unlike CPAP, use of oxygen in a 3-armed randomized controlled trial had no impact on 24-hour mean arterial pressure.[93] In a separate meta-analysis of randomized trials restricted to drug-resistant hypertension, the only difference to emerge with CPAP treatment was a −1.5 mm Hg diastolic nighttime fall.[94]

Potential explanations for such modest responses to therapy include conflation of hypertensive and sleepy participants with either normotensive or nonsleepy individuals, whose BP is influenced less by treatment[1,91,95]; insufficient adherence, particularly if CPAP is used only early in sleep, when the temporal burden of rapid eye movement (REM) sleep–associated OSA and the autonomic disturbances they elicit are least severe[90,96]; and use of discontinuous noninvasive ambulatory recording methods incapable of detecting the cyclic surges in systemic pressure accompanying each apneic event.[1] When BP was measured using continuous digital photoplethysmography in 36 randomized sleepy participants (58% hypertensive), therapeutic CPAP lowered average nighttime and daytime BP by 13/11 and 10/11 mm Hg, respectively.[97]

So as not to deny patients with OSA and EDS the symptomatic benefit of treatment, randomized trials of >3-month duration evaluating cardiovascular risk end points have, in general, restricted recruitment to nonsleepy participants. However, EDS is estimated to afflict only 20% with an AHI >5 (but women more frequently than men)[98] and 46% with an AHI >15.[99] As yet unknown is why the presence or absence of reported EDS should influence not only the likelihood of hypertension or insulin resistance associating with OSA but also

the BP and metabolic responses to CPAP treatment.[1,95,100] In 1 randomized trial of therapeutic versus nontherapeutic CPAP involving 35 nonsleepy individuals with OSA, 1-month treatment had no impact on 24-hour BP[101]; meta-analysis of trial results reveal a smaller BP response to PAP in those without EDS.[91]

In a Spanish cohort comprising 725 consecutive patients with an AHI ≥20 and an ESS ≤10, followed for a median of 4 years after randomization, CPAP did not reduce the incidence of new-onset hypertension. Incomplete CPAP adherence was offered as an explanation.[102] This interpretation is supported by a meta-analysis of 3 randomized controlled withdrawal trials. Each recruited only individuals using CPAP ≥4 hours per night. Two weeks after withdrawal, mean AHI increased from 3 to 33 and morning home BP rose, on average, by 9/8 mm Hg ($P$<0.001). In adjusted modeling, BP rose in parallel with AHI.[103]

## Pulmonary Hypertension

Mild or moderate pulmonary hypertension, in the absence of any evident alternate cause, can be detected in ≈20% to 40% of individuals with OSA, is associated with significantly shorter event-free survival, and can be reversed by effective CPAP treatment.[21,104] Both precapillary and postcapillary causal mechanisms have been identified. These include a greater propensity to venous thrombosis and pulmonary emboli and to pulmonary vascular remodeling induced by repetitive exposure to OSA-induced oscillations in arterial transmural pressure and oxygen saturation, reflex sympathetic excitation, and impaired LV relaxation.[21,105,106]

Relative to control subjects, individuals with OSA exhibit right ventricular hypertrophy and dilatation and impaired systolic function.[107] Daytime hypoxemia seems necessary for right HF.[108] Reduced right ventricular global and right lateral wall strain, proportionate to AHI, can be detected even when right ventricular ejection fraction itself is preserved.[109] In a cross-sectional evaluation of patients with stable pulmonary hypertension, those with coexisting OSA had higher pulmonary artery pressure, vascular resistance, and high-sensitivity plasma troponin-T concentrations, the latter consistent with subclinical myocardial injury.[110] One- to 4-month treatment of OSA with CPAP improved LV diastolic filling, reduced estimated pulmonary systolic pressure and vascular resistance, and attenuated hypoxic pulmonary vascular reactivity.[105,111] Thus, OSA is a potentially reversible cause of right ventricular dilatation and functional tricuspid regurgitation.

## Diabetes Mellitus

Several lines of investigation argue for an obesity-independent causal relationship between OSA and diabetes mellitus, a key cardiovascular risk factor.[112–114] In WSC participants with an AHI ≥15, the initial prevalence of diabetes mellitus was ≈8%, a 2.3-fold increase relative to those with an AHI <5, after adjustment for age, sex, and body habitus,[115] whereas in the SHHS cohort, at inception, proportions at these thresholds were 16% and 8%, respectively.[116] More recent studies report an association between the severity of OSA and HbA1c (hemoglobin A1c) in both nondiabetic and diabetic cohorts and estimate a prevalence of diabetes mellitus in those with moderate-to-severe OSA approaching 30%.[112,117,118] Conversely, ≥30% patients with type 2 diabetes mellitus will have an AHI ≥15.[112,119] The prevalence of OSA in type 1 diabetes mellitus is ≈50%; the majority of those affected do not profess daytime sleepiness.[120] Interestingly, by impairing tonic neural regulation of pharyngeal dilator muscles during sleep or by altering the hypercapneic drive to breathe, diabetes mellitus-associated neuropathy may raise the propensity of such patients to develop or worsen both OSA and CSA.[121,122]

Pancreatic β-cell dysfunction and progressive insulin resistance have been attributed to the inflammatory, sympathoadrenal, and humoral responses generated by the recurrent cycles of hypoxia, reoxygenation, and arousal with sleep fragmentation that characterize OSA.[77,112,114,123] Sleep fragmentation itself disrupts the synchrony between circadian hypothalamic clock and peripheral tissue metabolic gene expression.[6] The frequency of arousal correlates with increased efferent sympathetic vasoconstrictor discharge to skeletal muscle during wakefulness.[31] Observations such as a decrease in insulin-mediated forearm glucose uptake in response to an acute, reflexive, increase in upper limb NE release[124] and conversely, a reduction in insulin resistance with ganglionic blockade[125] argue for a causal relationship between sympathetic excitation and diabetes mellitus.

AHI and minimum oxygen saturation associate with insulin resistance, independent of BMI.[126] The SHHS investigators also identified significant independent associations between both the respiratory disturbance index and oxygen desaturation and the adjusted odds of impaired glucose tolerance.[127] The metabolic consequences of OSA are the most profound during REM sleep.[96,112]

Although a baseline AHI ≥15 did not increase the adjusted 4-year risk of developing type 2 diabetes mellitus in the WSC study,[115] the SHHS investigators reported a 1.71 increase in risk during a median 13-year follow-up, after AHI was adjusted for confounding factors.[128] Recent meta-analysis of studies of sleep disturbances aggregating data on >1 million subjects distilled, from those with OSA, a pooled relative risk for the development of diabetes mellitus of 2.2 (95% CI, 1.47–2.61).[129]

In cross-sectional studies, sleepiness also has emerged as an independent determinant of diabetes mellitus.[100] When individuals with OSA were dichotomized by the presence or absence of reported EDS and matched otherwise for age, BMI, and AHI, plasma glucose and insulin and insulin resistance were increased relative to healthy controls only in those with EDS. Treatment of OSA with CPAP improved these metabolic disturbances only in those with EDS.[100]

The present literature provides little definitive assurance that treating OSA will augment glycemic control.[113] In a randomized trial comparing therapeutic with subtherapeutic CPAP, 3 months of treatment had no impact on HbA1c, insulin resistance, or plasma adiponectin concentrations.[130] A meta-analysis of randomized controlled trials reported no significant effect of CPAP on HbA1c but greater sensitivity to insulin.[131] Adherence was the focus of a randomized trial involving prediabetic participants with an AHI ≥5 (mean AHI, 36) supervised overnight in a sleep laboratory. Two weeks of effective CPAP use (8 hours per night) reduced the frequency

of microarousal by 62%; lowered plasma glucose, NE concentrations, and average 24-hour BP; and augmented insulin sensitivity.[132] However, in a subsequent randomized trial involving 298 participants, 6 months of CPAP had no impact on HbA1c, regardless of adherence or baseline ESS.[133]

## Coronary Artery Disease

Recurrent hypoxia and reoxygenation compromise endothelial defenses against atherosclerosis by recruiting a phalanx of inflammatory responses: reactive oxygen species, cytokines, vascular and intracellular adhesion molecules, and proinflammatory transcription factors, such as NF (nuclear factor)-κB.[24,55,134] Individuals with OSA have fewer circulating endothelial progenitor cells and augmented endothelial cell apoptosis.[135] Their endothelial expression of eNOS and phosphorylated eNOS, plasma nitrate and nitrite concentrations, and brachial artery flow-mediated dilatation (the latter a sign of impaired NO bioavailability and a surrogate for endothelial integrity) are diminished, independent of obesity, whereas expression of nitrotyrosine and NF-κB is increased, with the latter disturbances reversible by 1 to 3 months of therapeutic CPAP.[136,137] Attenuated myocardial blood flow responses to dipyridamole infusion have been shown to normalize, along with endothelium-dependent and -independent dilatation, after 6 months of CPAP treatment.[138]

It has been difficult, from small cohort studies, to discern substantive differences in plasma lipid concentrations between those with and without this condition but in a meta-regression analysis, pooling data from 18 116 patients, plasma low-density lipoprotein, total cholesterol, and triglycerides were significantly greater in those with OSA; high-density lipoprotein cholesterol concentrations were lower.[139] AHI correlated inversely with high-density lipoprotein and positively with triglyceride concentrations but not low-density lipoprotein.[139] As yet, there is scant randomized controlled trial evidence that abolition of OSA improves lipids.[140] Enhanced low-density lipoprotein peroxidation has been detected in some individuals with moderate-to-severe OSA, but the impact of CPAP treatment on this atherosclerotic stimulus also has been inconsistent.[141,142]

OSA also is associated with increased plasma viscosity, fibrinogen concentration, hypoxia- and epinephrine-induced platelet activation, and attenuated fibrinolytic activity and disruption of their normal diurnal variation,[143–145] with PAI-1 (plasminogen activator inhibitor-1) activity and plasma alpha-2-antiplasmin concentration correlating significantly with AHI and minimum oxygen saturation.[144,146] In a randomized trial, 3 weeks of therapeutic CPAP did not normalize prothrombotic factor diurnal rhythms,[147] whereas in a randomized crossover trial of therapeutic versus placebo CPAP, enrolling 28 patients with severe OSA (mean AHI, 38), effective treatment reduced early morning vWF and nocturnal concentrations of coagulation factors VIII and V.[148]

Men and women aged ≤65 years with OSA are more likely than those without to manifest subclinical signs of atherosclerosis, such as coronary artery calcification, or to develop such with time.[56,149] A recent Korean cross-sectional study identified a significant association between coronary calcium score and the nadir of oxygen desaturation.[150] OSA increases the odds of having[151] (and in men, also the likelihood of developing) coronary artery disease.[152] In men aged 40 to 70 years in the SHHS cohort, whose AHI was ≥30, the adjusted likelihood of developing coronary artery disease after a median of 8.7 years was increased by 68%.[116] A subsequent meta-analysis confirmed this heightened risk to be specific to men.[153] OSA should be considered whenever a man or woman experiences the nocturnal occurrence of angina, an acute coronary syndrome, myocardial infarction, or sudden cardiac death.[8,9,47–49,57,154,155]

An intriguing body of evidence argues that recurrent hypoxia and reoxygenation also stimulate vascular endothelial growth factor,[156] mobilize endothelial progenitor cells,[135] and induce preconditioning responses that can preserve myocytes during ischemia or infarction. Clinical evidence for such cardioprotection in patients with OSA includes lower peak troponin-T concentrations,[157] more mature coronary collateral vessels,[158] and a predilection to non–ST-segment–elevation rather than ST-segment–elevation myocardial infarction.[159]

Nonetheless, several observational studies report fewer cardiovascular events in men and women if OSA is treated.[8,66,67] In a series of 431 patients with a documented LV ejection fraction (LVEF) >50% after mechanical or surgical revascularization, an AHI ≥15 was associated with an adjusted OR of 1.9 for impaired diastolic filling.[160] The Sleep and Stent Study investigators performed sleep studies on 1311 participants within 7 days of percutaneous coronary intervention; in 45%, the AHI was ≥15. OSA predicted independently major cardiovascular events accruing during a subsequent median 1.9-year follow-up.[161] In a retrospective study of individuals with documented OSA who subsequently underwent percutaneous coronary intervention, those treated with PAP experienced significantly fewer major cardiovascular events during the subsequent 5 years ($P$=0.027) and a trend toward lower all-cause mortality ($P$=0.058).[162] After myocardial infarction, OSA compromises recovery of ventricular systolic function and increases the likelihood of infarct expansion and adverse ventricular remodeling if left untreated.[53,54] The risk of recurrent cardiovascular events after an infarct is greatest in those with EDS, independent of AHI or oxygen desaturation.[163]

## Cerebrovascular Disease

OSA can increase the risk of both ischemic and embolic stroke by promoting inflammation, atherosclerosis, platelet activation, and a hypercoagulable state; triggering atrial fibrillation; and forcing transient opening of a patent foramen ovale. In a small imaging series, the prevalence of silent brain infarcts was 3-fold greater, relative to controls and accompanied by higher soluble markers of platelet activation in patients with moderate-to-severe OSA.[164] Hypertension and OSA exert independent and additive effects on carotid artery diameter and intima–media thickness—2 early signs of cerebrovascular disease.[165] In a cross-sectional comparison of 4 cohorts (with OSA, hypertension, both, or neither), multivariable analysis documented positive correlations between the AHI and both diameter and intima–media thickness.[165] In a randomized controlled trial of 4-month duration, treatment with CPAP reduced significantly carotid intima–media thickness, pulse wave velocity, a marker of conduit artery stiffness,

and C-reactive protein but not carotid diameter.[166] These observations are consistent with 2 concepts: OSA increases independently the risk of atherosclerosis, and effective treatment promotes its regression.

In the SHHS, having severe OSA increased the adjusted odds of having also experienced a stroke, by 58%.[152] Because OSA often is first appreciated after stroke, cross-sectional studies cannot establish whether OSA predisposes to or is a consequence of cerebrovascular infarction. In a cross-sectional analysis of 1475 subjects, OSA with an AHI ≥20 was associated with an adjusted OR for stroke of 4.33 (95% CI, 1.32–14.24; *P*=0.02), relative to those with an AHI <5, but in a cohort of 1189 followed for 4 years, the OR for incident first stroke was not significant after adjustment for age, sex, and BMI (3.08; CI, 0.75–12.81; *P*=0.12).[167] Yaggi et al[168] recruited 1022 untreated subjects, aged >50 years, without known prior myocardial or cerebral infarct who were referred for polysomnography for suspected SA. If the AHI was >5 (mean, 35), the adjusted HR for a composite end point comprising transient ischemic attack, stroke, or death after an average of 3.4 years was 1.97 (95% CI, 1.12–3.48; *P*=0.01). There was a dose–response relationship between the initial severity of OSA and composite end point occurrence (*P*=0.005). However, risk of stroke itself was not increased, and this end point incorporated CPAP-treated and untreated patients.

In the community-dwelling SHHS cohort, 5422 participants without a history of stroke were followed for a median of 8.7 years. Adjusted stroke-free survival in the top obstructive apnea–hypopnea index quartile was significantly worse in men (HR, 2.86; 95% CI, 1.1–7.4) but not in women. However, in the latter, an obstructive apnea–hypopnea index >25 did confer increased stroke risk.[169] In a subgroup analysis of Spanish men and women aged 70 to 100 years with severe OSA (AHI, ≥30), the adjusted risk of stroke occurring during the subsequent 6 years was 2.52 (95% CI, 1.04–6.01).[170] A Swedish series involving 392 coronary artery disease participants who underwent polygraphy and were then followed for 10 years calculated an adjusted HR for incident stroke (independent of diagnosed atrial fibrillation) of 3.56 (95% CI, 1.56–8.16).[171] A meta-analysis of trials with stroke as an end point identified a significant association between the AHI at baseline and subsequent events and an overall OR of 2.24 (95% CI, 1.57–3.19; *P*<0.00001). The risk for women was modest and not significant (1.21; CI, 0.65–2.25), whereas for men, the OR was 2.87 (95% CI, 1.91–4.31).[153]

The prevalence of sleep-related breathing disorders after stroke is high—60% for predominantly OSA and 12% for predominantly CSA.[172] After stroke, these phenotypes differ with respect to clinical import and pathogenesis, with only OSA increasing mortality risk, significantly, during 10 years of follow-up.[173] Among those who survive stroke, cognitive and functional status is considered worse if OSA is also present.[174] In a trial in which 140 patients with incident stroke and an AHI ≥20 were randomly allocated CPAP, cardiovascular survival was significantly greater, at 5 years, in the treated group.[175]

## Arrhythmias

Patients with OSA are prone to vagally mediated episodes of sinus bradycardia and arrest and atrial–ventricular block during sleep. The frequency of such events is attenuated markedly by effective use of CPAP.[176,177] Even in the absence of profound pauses, apnea during sleep can entrain both sinus variation and the ventricular response to atrial fibrillation to these cycles' very low frequency (<0.04 Hz).[178,179] When awake and breathing spontaneously, patients with moderate-to-severe OSA exhibit, relative to control subjects, higher heart rate and MSNA burst frequency and at the same time, less R-R interval variance in the time domain, a decrease in high frequency (vagal) heart rate modulation, and an increase in low-frequency heart rate variability.[180] In longitudinal studies, each of these disturbances has predicted foreshortened life expectancy.[61] Of note, paradoxically low heart rate variability, in the context of slow heart rate, increases the risk of developing atrial fibrillation.[181]

Over the last 2 decades, the interrelationship between OSA and atrial fibrillation has emerged as one of particular clinical importance.[18,182] In the absence of HF, OSA is more prevalent (in up to 80%) in those with paroxysmal or persistent atrial fibrillation than in reference groups.[183] Only the minority of patients with both conditions report EDS,[184] but those who experience both atrial fibrillation and OSA report more rhythm-related symptoms and are at higher risk of hospitalization than those without documented apnea.[182] CSA is also detected more frequently when atrial fibrillation is present and ventricular systolic function is preserved.[185]

Acutely, the confluence of hypoxia, autonomic imbalance, and wall stretch induced by an abrupt reduction in intrathoracic pressure can initiate atrial arrhythmias.[186] In a canine model, hypoxemia alone was insufficient to trigger atrial fibrillation. To do so required superimposition of acute reductions in intrathoracic pressure, which distends the atria, shortens atrial effective refractory period, and increases fibrillation vulnerability.[187,188] Its induction can be attenuated by both autonomic blockade and radiofrequency ablation of the right pulmonary venous ganglionic plexus.[189] Chronic exposure to obstructive apneas alters atrial tissue, electric, autonomic, and conductive properties, increasing the probability that OSA-induced changes in autonomic input and wall tension will trigger atrial ectopy, activate atrial drivers, and induce the rotors and dynamic reentry circuits responsible for initiating and sustaining atrial fibrillation.[186] Comorbidities such as diabetes mellitus or hypertension amplify such proarrhythmic mechanisms.[190]

In an Olmstead County series, incident atrial fibrillation correlated significantly with OSA-induced decreases in nocturnal oxygen saturation but only in patients <65 years of age.[191] SHHS participants with OSA and a respiratory disturbance index ≥30 had a 4-fold higher prevalence of atrial fibrillation (adjusted OR, 4.02; CI, 1.03–15.75) than those without.[183] However, incident atrial fibrillation, during a 5.3-year mean follow-up was predicted by CSA, not OSA.[192] A longitudinal study involving elderly men yielded similar conclusions.[193] Atrial mechanical or electrophysiological features of CSA may be responsible. Significantly lower left atrial reservoir, conduit, and contractile phasic function in HFrEF patients with CSA than with OSA[194] may render the former more prone to fibrillation. In an ovine experiment, hyperventilation-induced hypocapnia induced selective shortening of the effective refractory period but not conduction velocity, whereas hypoxia had no significant effect on the effective

refractory period, atrial conduction time, or vulnerability to atrial fibrillation.[195]

OSA is a common cause of failure to maintain sinus rhythm after initially successful cardioversion or ablative intervention.[196–199] This risk may relate to persistent, unaddressed, nocturnal hypoxemia,[191,196] which augments reflexively efferent parasympathetic and cardiac sympathetic nerve firing. In a series of patients with atrial fibrillation referred to the Mayo Clinic for electric cardioversion, OSA was detected in 49%.[200] After cardioversion, there was a significantly higher recurrence rate in those with untreated OSA and hypoxia.[196] OSA (mean AHI, 27) has been detected in 87% of patients whose atrial fibrillation returned after initially successful pulmonary vein isolation.[198] In a multisite evaluation of 3000 consecutive patients referred for this procedure, those with untreated OSA were ≈9× more likely to redevelop atrial fibrillation than those so treated.[197] A meta-analysis incorporating data from 3995 patients from 6 pulmonary vein isolation studies concluded that polysomnography-diagnosed OSA increases this risk by 40%.[199]

In addition to preventing the noxious chemical and noradrenergic consequences of OSA, chronic CPAP use also may reduce susceptibility to atrial fibrillation by decreasing wall tension, permitting reverse atrial remodeling, and normalizing total conduction time.[201] In a Japanese cohort, CPAP treatment reduced, significantly, the occurrence of paroxysmal atrial fibrillation during sleep,[177] and in the ORBIT-AF registry, those using CPAP were 34% less likely to develop permanent atrial fibrillation.[182] Risk factor management, including suppression of OSA with CPAP, can improve arrhythmia burden and maintenance of sinus rhythm following ablative procedures.[202] In a series of 426 patients who underwent both pulmonary vein isolation and polysomnography, atrial fibrillation recurred in those with treated OSA at a rate similar to that observed in patients without OSA; if OSA was untreated, the rate of recurrence after ablation was similar to that documented in individuals with OSA who did not undergo this procedure.[203]

In summary, chronic exposure to SA and its sequelae can alter atrial substrate, increasing the susceptibility to fibrillation; because obstructive apnea is a sleep-specific event, the arrhythmias it induces are more likely than not to be asymptomatic and risk provoking cryptogenic stroke; patient symptoms are unreliable for diagnosis because the majority with atrial fibrillation- and sleep-related breathing disorders is not sleepy; and the coexistence of OSA will complicate contemporary interventional atrial fibrillation management. Individuals who wake without sensing dysrhythmia are unlikely to seek medical attention, thereby increasing their risk of subsequent stroke or HF. Importantly, despite such accumulating evidence for sleep-disordered breathing (SDB) as a causal mechanism, neither OSA nor CSA is considered in contemporary atrial fibrillation formulae informing anticoagulant prescription to prevent stroke.

In the SHHS cohort, OSA increased the risk of nonsustained ventricular tachycardia by >3-fold and the risk of complex ventricular ectopy by 74%.[183] In a cohort of men aged >65 years, the frequency of complex ventricular ectopy was a function of hypoxia severity.[46] In a large longitudinal Mayo Clinic cohort, sudden cardiac death associated with age >60 years, AHI >20, and mean nocturnal $O_2$ saturation <93%.[49] However, a recent systematic review could not affirm definitive links between ventricular tachycardia or fibrillation and OSA or attenuation of these potentially lethal arrhythmias by CPAP.[204]

## Heart Failure

In a canine model of OSA, 1 to 3 months of intermittent airway occlusion during sleep increased LV end-systolic volume and reduced LVEF.[205] In the SHHS study, risk-adjusted prevalence of HF with baseline OSA and an AHI ≥11 increased 2.38-fold relative to those without OSA[152]; over an 8.7-year median follow-up, men without history of this condition who had an AHI ≥30 were 58% more likely to be diagnosed with HF relative to those whose AHI was <5. Such risk was not increased in women.[116,169] Men may be more vulnerable because of their muscular capacity to generate, on average, more negative intrathoracic pressure and hence LV afterload, with each obstructive event. In elderly men (mean age, 76 years), it was the presence of cycles of CSR cycling persisting >10 minutes, rather than OSA, that predicted incident HF.[206] Despite such data, SA has yet to be incorporated into HF risk prediction models.[207]

Sleep-disordered breathing with an AHI ≥15 has been detected by polysomnography or polygraphy in >80% of patients hospitalized with acute decompensated HF,[208,209] in ≈50% of patients with chronic HFrEF receiving contemporary drug and device therapy,[35,210–212] and in a similar proportion of HF patients with preserved LVEF.[34,185] AHI >5 can be detected in ≈80% with chronic HF, regardless of ejection fraction.[34]

Peripheral edema contributes mechanistically to the high prevalence of SA in HFrEF. Overnight, fluid shifts rostral into the chest, initiating CSR by stimulating hyperpnea, and into jugular veins and peripharyngeal tissues, increasing upper airway resistance and propensity to obstruction[8,45] (Figure 3). In the acute setting, OSA predominates,[208,209] presumably because of increased intravascular and extravascular peripharyngeal fluid during recumbence and sleep.[213] With resolution of congestion and improved ventricular systolic function, the prevalence and severity of OSA diminishes.[214] In chronic stable patients, 1 form of SA dominates, but up to 40% of patients may exhibit a mixed picture, in which the nondominant disorder generates up to 20% of nocturnal events.[43]

SDB affects proportionately more men than women with HFrEF.[215] In women, SDB is predominantly obstructive[43]; CSA with CSR is uncommon.[38–41,210,215] In men with HFrEF, each of age >65 years, atrial fibrillation, ventricular pacing, hypocapnia (arterial $PaCO_2$, <38 mm Hg), low BMI and systolic BP and clinical symptoms and signs and biochemical markers of advanced HF increase the likelihood of coexisting CSA.[41,43,210] At the bedside, the observant clinician can estimate cardiac output by timing the duration of hyperpnea.[216] As with OSA,[27,30] the majority of HFrEF patients with CSA does not profess sleepiness[38,39,215]; their average ESS scores are also lower than those with HFrEF and OSA.[215]

Untreated sleep-disordered breathing confers an independent adverse prognosis on those presenting with acute decompensation[208,209] or followed for chronic stable HF, with more frequent readmission to hospital and foreshortened life

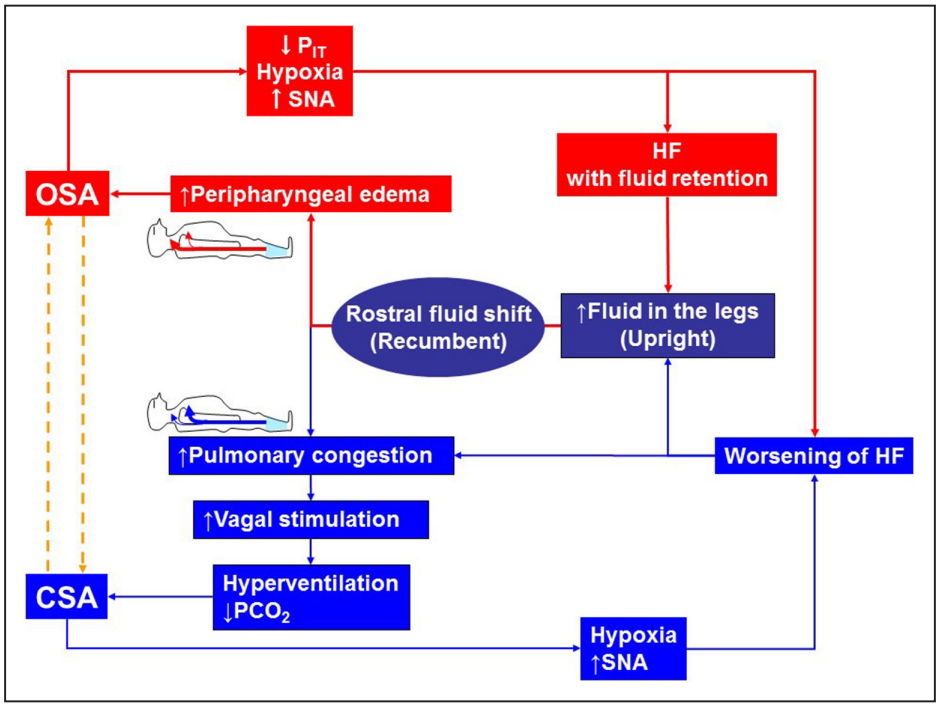


**Figure 3. Postulated bidirectional relationship between sleep apnea and heart failure (HF).** Confluence of intermittent hypoxia, elevated sympathetic nervous system activity (↑SNA) and reduced intrathoracic pressure (↓$P_{IT}$) promotes HF development or progression and HF-related sodium and fluid retention. Rostral shift of fluid when supine into peripharyngeal structures can induce or worsen obstructive sleep apnea (OSA); rostral shift of fluid into the chest can induce or worsen central sleep apnea (CSA). Reprinted from Kasai et al[8] with permission. Copyright ©2012, the American Heart Association.



expectancy.[8,45,217–219] Observational studies conducted in the era of contemporary HFrEF drug and device therapy report significantly worse 4-year survival when moderate-to-severe SDB coexists[212]; adjusted risk mortality doubles if either CSA[218] or OSA[217] is present, yet untreated. Obstructive apnea is specifically a sleep-related event but central apnea with CSR is not. The latter's presence during wakefulness, in conjunction with HFrEF, is particularly ominous, predicting lower cardiac output, higher filling pressure, augmented peripheral chemoreceptor sensitivity, and foreshortened life expectancy.[40,220]

Whereas normal LV contractile function is relatively unperturbed by simulated OSA, the abrupt increase in LV afterload and drop in preload during each obstructive event causes stroke volume and systolic BP of patients with HFrEF to fall and remain depressed postapnea until elevated by the subsequent reflex wave of sympathetically mediated inotropy and vasoconstriction.[14] During the course of sleep, an obstructive apnea lowers stroke volume by 7% on average, whereas a central apnea is accompanied by a 3% mean increase[221] (Figure 4).

The time during which the ventricle is exposed to an oxygen saturation <90% ($TST_{90}$) confers greater adverse risk than the AHI per se, with a 5-year survival probability of only 50% for those at the lowest saturation quartile.[222] In a Japanese series, the portion of recording time during which oxygen saturation fell ≥4% from baseline was superior to both the AHI and $TST_{90}$ as an independent predictor of premature mortality.[223] Another adverse prognostic sign is chemoreceptor sensitization, which augments reflex control of ventilation and sympathetic neural responses to hypoxia or hypercapnia; attenuates baroreceptor-mediated vagal modulation of heart rate; entrains oscillations in BP, heart rate, and sympathetic outflow; incites ventricular ectopy; and presages premature death.[61] In a prospective study that exposed patients with HFrEF to hypoxia and to hypercapnia, the 28% of the cohort with exaggerated responses to both stimuli had a 4-year survival of 49%, compared with 100% in the 39% with normal chemoreflex responses.[224]

Sustained sympathetic nervous system activation and attenuated parasympathetic heart rate modulation, with loss of circadian variation in autonomic tone, are extensively documented markers of premature mortality in the HFrEF population.[61] Coexisting sleep-disordered breathing tips this balance toward persistent sympathetic dominance after awakening from sleep.[58] For OSA, such upward resetting of sympathetic outflow has been attributed to augmented carotid chemoreceptor afferent signaling and to altered structure and synaptic function within cortical and brain stem regions involved in cardiovascular regulation in response to recurrent hypoxemia, inflammation, and sleep fragmentation,[31,59,60] whereas in CSA, sympathetic excess generally reflects more severe HF, with higher pulmonary capillary wedge pressure, lower cardiac index, and significant positive relationships between cardiac and total body NE spillover and pulmonary capillary wedge pressure and mean pulmonary artery pressure.[43,44,210] If AHI exceeds 15, impaired cardiac sympathetic neurotransmitter uptake also is significantly more common and predicts worse survival.[225]

Adding adverse mechanical loading renders this substrate conducive to atrial fibrillation and lethal ventricular arrhythmias.[17] In 1 series comprising 283 HFrEF patients followed for 54 months after receiving a cardiac resynchronization device wtih defibrillator capacity, the risk of an appropriate discharge

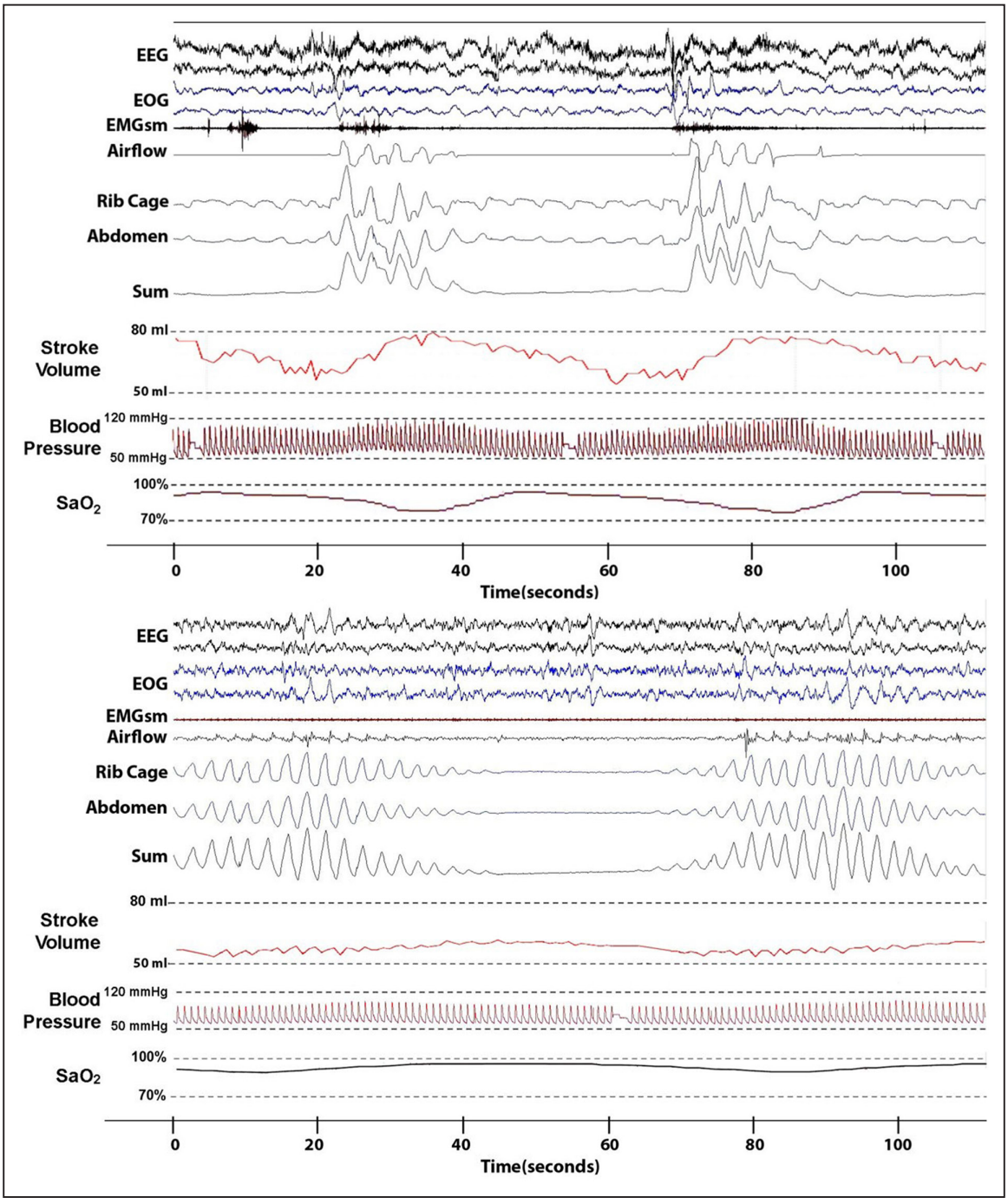


**Figure 4. Polysomnographic recordings from a 60-y-old man with heart failure (left ventricular ejection fraction, 40%) who develops both obstructive (top) and central (bottom) apnea during the course of a single night**. During the obstructive apnea, digital photoplethysmography-derived stroke volume falls, whereas in contrast stroke volume increase during central apnea, it rises. Reprinted from Yumino et al[221] with permission. Copyright ©2013, American Thoracic Society. EEG indicates electroencephalogram; EMGsm, submental electromyogram; EOG, electrooculogram; and $SaO_2$, arterial oxygen saturation.

was 2-fold greater in those with untreated SDB and an AHI ≥15 relative to those without apnea. On average, if the disorder was OSA, the first such discharge occurred 17 months sooner and if CSA, 25 months sooner than if SDB was absent.[226] In the latter, ventricular ectopy clusters during the hyperpneic phase of CSR.[227] A systematic review comprising 9 such studies estimated a 55% increased risk (95% CI, 34%–83%), similar in those with CSA and OSA, of appropriate cardioverter–defibrillator therapy if SDB was present.[228] In patients with ischemic cardiomyopathy, this propensity to lethal arrhythmia may account for a 3-fold greater adjusted risk of mortality if moderate-to-severe SDB is present but untreated.[219]

With contemporary evidence-based drug and device therapies having little or no mitigating effect on the acute- or long-term mechanical, chemical, autonomic, inflammatory, or cardiometabolic consequences of sleep-disordered breathing, alternate treatment

strategies targeting specifically breathing disorders to enable recovery of ventricular systolic function have been pursued. For OSA, this is straightforward—splinting of the upper airway by effective CPAP abolishes obstructive apneas and its adverse consequences immediately.[229] Observational studies identified significantly better survival in patients with OSA and HFrEF who adopted CPAP,[212,217] particularly if adherence was good.[230] Nonetheless, a reluctance to deny such patients effective therapy for EDS has inhibited long-term randomized trials in this population. Initial protocols were brief and recruited generally nonsleepy patients yet demonstrated, with elimination of OSA and its cardiotoxic accompaniments, recovery of LVEF, improved myocardial retention of $^{11}$C-hydroxyephedrine (ie, restoration of sympathetic neurotransmitter reuptake) and myocardial work metabolic index and concurrent reductions in BP, heart rate, frequency of ventricular ectopy, and MSNA.[45,231–233] Importantly, in the course of such research, it became evident that the majority of patients with HFrEF and OSA were not sleepy.[27,30,215] An inverse relationship between the ESS score and MSNA[234] suggests that treating OSA might exert more cardiovascular benefit in nonsleepy patients.

Randomized trials of CPAP in patients with HFrEF have documented, after 3 months of effective treatment, improvements in LVEF and reported quality of life and reductions in mitral regurgitation, overnight urinary NE excretion, and daytime plasma NE concentration and after a median of 2.2 years, an 81% improvement in transplant-free survival in adherent individuals.[45] However, CPAP fails to suppress CSA in ≈50% of patients with HFrEF experiencing this breathing disorder.[235]

Adaptive servo ventilation (ASV), which senses hypopneas or apneas and adjusts pressure support according to tidal volume or airflow-based algorithms, suppresses CSA more effectively than CPAP.[236] To prevent OSA, sufficient pressure to maintain upper airway patency is administered continuously. In a randomized comparison against CPAP, both efficacy and adherence were superior with peak flow-triggered ASV.[237] In the Bad Oeynhausen registry cohort with HFrEF and implanted defibrillators, ASV-treated patients with CSA–CSR experienced significantly fewer arrhythmic events than those who declined therapy; event-free survival in the former subgroup was comparable with that of individuals without CSA–CSR.[238] Small randomized trials have documented a fall in AHI, New York Heart Association class, and plasma BNP (B-type natriuretic peptide) concentrations, a rise in LVEF, improved cardiac $^{123}$I-metaiodobenzylguanidine imaging kinetics, and fewer hospital readmissions in those allocated effective therapy.[239,240]

ASV's potential in HF patients with preserved LVEF is less studied. In a trial involving 36 patients with HF, LVEF >50% and an AHI >15 randomized to 6 months of ASV and then followed for a further year, symptom class, left atrial volume, BNP concentration, ventricular filling, and event-free survival all improved in those so treated.[241]

## Randomized Trials With Cardiovascular End Points

### OSA Without HF

#### *Spanish Sleep and Breathing Network Trial*

In this cohort of 725 consecutive patients with an AHI ≥20 (by conventional polysomnography or a cardiorespiratory sleep study) and an ESS ≤10, followed for a median of 4 years, CPAP prescription did not reduce a composite outcome that included the incidence of cardiovascular events and new diagnosis or treatment of hypertension. With only 57 events recorded, the investigators conceded insufficient statistical power but offered post hoc secondary subgroup analyses. The primary composite end point was reduced significantly in those who used CPAP ≥4 hours per night, particularly if nocturnal oxygen desaturation was attenuated.[102]

#### *Randomized Intervention With CPAP in Coronary Artery Disease and OSA*

To determine the effect of long-term CPAP treatment initiated after mechanical or surgical revascularization, 244 consecutive patients with an AHI ≥15, ESS <10, and an average LVEF of 56% were randomly allocated auto-titrating CPAP or no PAP and followed for a median of 57 months. A 20% reduction in cardiovascular end points in the group prescribed CPAP was nonsignificant ($P$=0.45), but in those who used CPAP for ≥4 hours each night, the adjusted event rate fell by 71% (HR, 0.29; 95% CI, 0.10–0.86; $P$=0.026).[151]

#### *SAVE*

The SAVE study (Sleep Apnea Cardiovascular Endpoints) tested the hypothesis that CPAP would reduce the occurrence of a composite of death from cardiovascular causes, myocardial infarction, transient ischemic attack or stroke, or hospitalization for HF or an acute coronary syndrome.[242] A cohort of 2717 participants aged 45 to 75 years with moderate-to-severe OSA (≥12 episodes per hour of $O_2$ desaturation from baseline of ≥4% diagnosed not by polysomnography but via home screening with oximetry, nasal pressure recordings, and automated signal analysis), an ESS ≤15, and preexisting coronary or cerebrovascular disease was enrolled. After a mean 3.7-year follow-up of 2687 subjects, CPAP reduced snoring and daytime sleepiness and improved mood and health-related quality of life but had no effect on the cumulative occurrences of the composite end point (HR, 1.10; 95% CI, 0.91–1.32; $P$=0.32) or any of its individual elements. The investigators concluded that adding CPAP did not prevent cardiovascular events in patients with moderate-to-severe OSA and preexisting disease.

Several limitations were acknowledged. Investigators anticipated enrolling 5000 participants. Individuals with $Pao_2$ <80% during >10% of time recorded or with an ESS >15, who might have benefited the most from effective treatment, were excluded. Reported adherence was on average 3.3±2.3 hours, and use was primarily during the early hours of sleep, whereas REM sleep-related desaturation and desaturation time during apneas and hypopneas are amplified through its later hours.[96] A prespecified analysis observed that use of CPAP ≥4 hours per night suggested a reduced rate of stroke (unadjusted HR, 0.56; 95% CI, 0.32–1.00; $P$=0.05).

In summary, current clinical trial evidence is neutral; patient recruitment has been selective, out of concern that participants could experience unaddressed EDS for many years; and therapy has been only partially effective. Consequently, equipoise remains, regardless of ESS, as to whether optimal adherence to effective overnight suppression of OSA with PAP will reduce cardiovascular morbidity, hospitalization, or death.

## Sleep-Disordered Breathing and HF

### CANPAP

The multicenter CANPAP trial (Canadian Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure) aimed to test the hypothesis that CPAP treatment would improve transplant-free survival of HFrEF patients with CSA.[38] During the course of the trial, widespread clinical adoption of β-adrenoceptor and mineralocorticoid receptor blockade resulted in a lower than anticipated event rate. Projecting futility, the Data Safety Monitoring Committee recommended termination after 258 participants (mean LVEF, 24.5%; AHI, 40 by polysomnography), all stable on optimal contemporary medical therapy, had been randomized to receive, in addition, therapeutic CPAP and followed for a mean of 2 years. Average nightly adherence (at ≥1 year, 3.6 of 5 hours) exceeded expectations. Relative to control patients, there were greater reductions in AHI (−21 versus −2 events per hour; $P<0.001$) in the treated group. Surrogate end points, such as nocturnal $O_2$ saturation, and daytime LVEF, plasma NE concentrations, and 6-minute walk distance all improved. Transplant-free survival was identical, but the impact of treatment appeared dichotomous, with early harm in some yet long-term benefit in the remainder.

As a test of its hypothesis, the CANPAP trial was thus neutral. However, in 43% of participants allocated treatment, polysomnography at 3 months revealed an AHI >15 (ie, above the trial's entry criterion). Because CPAP was so ineffective, CANPAP could not test definitively the hypothesis that suppressing CSA in HFrEF improves transplant-free survival. Post hoc analysis yielded an encouraging signal: if the AHI fell <15, transplant-free survival with treatment was improved significantly, relative to untreated control participants (HR, 0.37; 95% CI, 0.14–0.97; $P=0.043$), and there was greater recovery of ventricular systolic function ($P=0.001$).[235]

### SERVE-HF

The SERVE-HF (Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure) investigators recruited chronic HFrEF patients (LVEF, ≤45%) with New York Heart Association class III or IV symptoms or class II symptoms but with an HF admission in the prior 2 years, who were identified by home polygraphy (and in some instances in-laboratory polysomnography) to have an AHI >15 with predominantly (≥50%) CSA and central AHI ≥10.[39] Participants were allocated randomly, according to an open-label study design, either to continue guideline-based medical therapy or, in addition, use minute volume of ventilation-triggered ASV (mv-ASV) for >5 hours per night. The primary study end point was a composite of death from any cause, cardiac transplantation, LV assist device implantation, resuscitation after sudden cardiac death, appropriate defibrillator discharge, or unplanned admission for worsening HF. The trial design anticipated 651 events in 1193 patients; recruitment was extended until 1325 participants were secured.

On enrollment, 69% were classified as having class III symptoms. After the first 3 months, subjects were followed annually. There were 695 primary events during a mean of 2.6 years. The Data Safety Monitoring Committee, which conducted 2 interim reviews for 7 years, did not recommend early termination. The initial published analysis,[39] according to intention-to-treat allocation, was neutral with respect to the primary end point (HR if randomized to mv-ASV, 1.13; 95% CI, 0.97–1.31; $P=0.10$). Reductions in both ESS ($P<0.001$) and 6-minute walk distance ($P=0.02$) were greater in those assigned mv-ASV, but otherwise there were no between-group differences with respect to symptoms, ventricular structure or function, renal function, plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations, or inflammatory markers.[39,243] However, in those allocated mv-ASV, the HRs for 2 secondary end points, all-cause (1.28; 95% CI, 1.06–1.55; $P=0.01$) and cardiovascular mortality (1.34; 95% CI, 1.09–1.65; $P=0.006$), were increased.[39] The trial investigators concluded that addition of mv-ASV to guideline-based medical therapy did not improve the outcome of HFrEF patients with predominantly CSA and increased the risk of cardiovascular death but conceded that these findings might not pertain to treatment of CSA with other ASV algorithms. They emphasized that the SERVE-HF results could not be extrapolated to HFrEF patients with predominantly OSA.

Factors influencing cardiovascular mortality were age, male sex, ischemic pathogenesis, diabetes mellitus, higher New York Heart Association class, longer $TST_{90}$ and QRS duration, lower BMI, LVEF, and glomerular filtration rate, and a greater proportion of the total AHI classified as CSR.[244] To determine effects on discrete elements of the primary composite end point, the investigators performed multistate modeling, also based on group allocation. Risks for both cardiovascular death without preceding hospital admission (HR, 2.59; 95% CI, 1.54–4.37; $P<0.001$) and cardiovascular death after a life-saving event (HR, 1.57; 95% CI, 1.01–2.44; $P=0.045$) were increased in those randomized to mv-ASV. Participants with low baseline LVEF (≤30%) and with CSR evident through >50% of the recording period, and thus likely the most unstable medically, were at greatest risk of cardiovascular death without prior admission. Conversely, the risk of hospital admission for worsening HF was significantly lower if LVEF exceeded 30% or if the burden of CSR was low (occurring <20% of recording time).[245] This proportion could signify a substantial contribution of obstructive events without CSR to the total AHI, fewer hours of sleep, or higher cardiac output.[216]

The initial published findings inspired vigorous debate as to whether the SERVE-HF trial results were definitive, its secondary end point findings condemn all modes of PAP therapy for CSA, and CSR with CSA is compensatory rather than maladaptive.[221,246]

Concerning the trial, itself, diagnosis and severity of central apnea were determined locally using home polygraphy (which does not capture actual sleep time) rather than by formal polysomnography. Without review by a core laboratory, classification of central and obstructive hypopneas may have differed across sites. A number of HF patients with preserved LVEF were enrolled. Concerning adherence, average mv-ASV use was 3.7 hours per night, but only 60% of those allocated mv-ASV applied wore this device for ≥3 hours per night, 29% discontinued its use, and 17% of the control group initiated some form of positive pressure ventilation. Such crossover suggested that in some instances, patient or physician preferences may have superseded the trial protocol, prejudicing its conclusions. This question was the subject of a time-dependent on-treatment analysis.[244] Outcomes

cohered with the original allocation: those who abandoned mv-ASV remained at higher risk of cardiovascular death than controls, whereas those who adopted mv-ASV tended to maintain a lower risk for this end point than those initially assigned treatment. Analysis based on treatment used during all follow-up periods, regardless of initial group, revealed no increase in cardiovascular risk (adjusted HR, 1.09; 95% CI, 0.88–1.35; *P*=0.44); 1 of borderline significance if based on adherence to the randomization arm (1.27; 95% CI, 1.00–1.62; *P*=0.051), and 1 with narrower CIs if baseline risk was considered (1.28; 95% CI, 1.01–1.63; *P*=0.043). Importantly, cardiovascular risk did not parallel nightly hours of use. Whether events occurred when participants were asleep or awake (when mv-ASV use would be unlikely) was not reported.[244]

Uncertainty remains as to whether the secondary end point findings in SERVE-HF condemn all modes of ASV or are a specific consequence of the first-generation proprietary device used. In SERVE-HF, ASV treated CSA based on minute ventilation but lacked an algorithm to alleviate obstructive events automatically (expiratory airway pressure could be modified manually). Downloaded data revealed, in many participants, a greater proportion of obstructive events causing desaturation.[39] The relatively high introductory default expiratory PAP and minimum inspiratory pressure support settings (5 and 8 cm $H_20$, respectively) may have lowered the stroke volume of euvolemic participants,[247] leading to hypoperfusion and more unstable breathing.[216,248] Metabolic adaptations to the chronic hyperventilation generated by a minute ventilation algorithm could promote ventricular arrhythmias. As per protocol, mv-ASV was introduced using a full face mask, which risks lower compliance and encourages $CO_2$ rebreathing.[248]

### *CAT-HF*

The objective of the CAT-HF trial (Cardiovascular Improvements With MV-ASV Therapy in Heart Failure) was to determine whether mv-ASV improved cardiovascular outcome of patients hospitalized for acute decompensation, regardless of LVEF, whose AHI by polygraphy was ≥15. This trial was terminated with 126 of the planned 215 participants recruited. At 6 months, average daily adherence was only 2.7 hours. There were no between-group differences with respect to any prespecified outcome.[249]

### *ADVENT-HF*

The ADVENT-HF trial (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure), a parallel-group, open-label trial, is enrolling stable, optimally treated patients with HFrEF (LVEF, ≤45%) identified by polysomnography as having either form of SDB with an AHI ≥15.[250] Unlike SERVE-HF, participants first are evaluated by precertified echocardiography and sleep facilities, with data transferred to core laboratories for review and validation and then stratified into 2 groups (≥50% of events obstructive, but not sleepy [ESS, ≤10], or ≥50% of events central) before 1:1 randomization to continued optimal medical therapy or the addition of peak flow-triggered ASV algorithm, applied via a nasal mask, with default expiratory and minimum inspiratory pressure support settings of 4 and 0 $cmH_2O$, respectively. Polysomnography is repeated after 1 month to ensure that peak flow-triggered ASV has lowered the AHI <15. If not, a retitration study is scheduled; the subject is withdrawn if AHI remains >15. Participants are followed every 3 to 6 months for 5 years. The trial's primary outcome is a composite that includes all-cause mortality and cardiovascular hospital admissions. To date, 557 of an anticipated 860 patients have been randomized. Of these, the majority has predominantly OSA and New York Heart Association class II symptoms.

Important distinctions between ADVENT-HF and SERVE-HF include less symptomatic participants, recruitment of HFrEF patients with OSA (but not sleepy) and CSA, data validation by core laboratories on enrollment and during follow-up, application of a peak airflow-triggered algorithm shown to suppress OSA as well as CSA, lower expiratory and inspiratory default pressures, predominant use of a nasal rather than a full face mask, superior nightly adherence, thus far, and more frequent clinical and safety review.[250] The Data Safety Monitoring Committee has examined data separately for patients with OSA and CSA on 5 occasions since the SERVE-HF announcement and recommended continued per protocol enrollment. ADVENT-HF is thus the sole active trial capable of resolving present clinical equipoise concerning the cardiovascular and mortality benefits of suppressing either form of SA in HFrEF.

**Table 3. Proposition: Sleep-Disordered Breathing Should Be Treated to Reduce Cardiovascular Risk**

| Pro | Con |
|---|---|
| High prevalence | Neutral results of large randomized trials of partially effective therapy |
| Apnea-induced events increase hemodynamic load and induce cardiometabolic pathology, central neuroplasticity, and peripheral autonomic imbalance | Increased risk of cardiovascular secondary end points specific to treating Cheyne–Stokes respiration with central apnea and low LVEF using mv-ASV |
| Adverse cardiovascular clinical consequences | |
| Increased risk of premature death | |
| Current drug or cardiovascular device therapy fails to counter key pathology or attenuate risk | |
| Encouraging observational data | |
| Positive results of small-sized short-term randomized trials of effective therapies involving surrogate end points | |

LVEF indicates left ventricular ejection fraction; and mv-ASV, minute ventilation-triggered adaptive servo ventilation.

**Table 4. Clinical Uncertainties**

| Entity | Question | Rationale |
|---|---|---|
| Adherence | Can this be improved? | Consistently fewer cardiovascular events if >4 h per night PAP use. Poor adherence common to all large clinical trials with cardiovascular end points. |
| Age | Should SDB treatment target younger individuals? | Opportunities to reverse may be greater.<br>Magnitude of benefit appears less in elderly. |
| Alcohol | Is alcoholic cardiomyopathy a true entity or is this simply secondary to alcohol-induced OSA? | Alcohol increases upper airway resistance and collapsibility, increasing AHI. Abstinence improves AHI. Improved AHI associated with LVEF recovery. |
| Aortic dilatation | Should patients with aortic dilatation or dissection be referred for PSG? | Potentially reversible cause of aortic dilatation.<br>Increased aortic wall stress induced by repetitive acute profound reductions in intrathoracic pressure could trigger dissection. |
| Atrial fibrillation | Should patients who wake with atrial fibrillation be referred for PSG?<br>Should patients with atrial fibrillation be investigated and treated for OSA before elective cardioversion or ablative therapy?<br>Should OSA be incorporated into stroke risk scores? | Long-term electrocardiographic monitoring and smartphone ECG apps will detect more nighttime and daytime paroxysms of uncertain significance. |
| Cardiac regenerative therapy | Should all patients receiving such therapies undergo polysomnography?<br>Should randomized trials of cardiac regenerative therapy stratify patients based on the presence or absence of OSA before randomization? | Results of trials involving small numbers may be confounded by greater impact of coexisting untreated OSA on ventricular systolic function than the intervention itself. |
| Drug therapy | Can SDB- or SDB-mediated increased chemoreflex sensitivity be modified pharmacologically? | Inhibition of peripheral chemoreflex by adenosine antagonists, angiotensin receptor blockade. Central actions of $\alpha_2$ agonists. Pharmacological modulation of upper airway tone. |
| Hypertension | Why are all with OSA not hypertensive?<br>Why are some sleepy and others not?<br>What is the mechanism for hyperaldosteronism?<br>Why are apparent treatment effects so modest?<br>Why should daytime sleepiness determine whether treatment lowers BP?<br>What reduces cardiac risk more—a 2–3 mm Hg fall in BP or regression of LVH because of abolition of recurring surges in transmural LV pressure (afterload)?<br>Can effective renal denervation attenuate OSA sympathetically mediated reductions in renal blood flow, renal sodium retention, or renin–angiotensin–aldosterone system activation? | Increased central sympathetic outflow during sleep and wakefulness should increase NE release, vascular resistance, and cardiac output. Countered by altered neurovascular transduction?<br>Greatest reductions seen if BP is measured continuously. |
| Risk estimates | Should OSA be included in formulae estimating cardiovascular or stroke risk? | The independent risks established for OSA are not presently incorporated. |
| Screening | If most affected are asymptomatic, what is the most effecient/effective means of detecting SDB?<br>How can selection bias be avoided in clinical trials? | Majority of individuals with moderate or severe SDB and cardiovascular disease are neither obese nor sleepy and thus not detected by these criteria. |
| Severity | What is the best measure of apnea severity?<br>Should all future epidemiological surveys, observational studies, and clinical trials incorporate standard measures? | Methodological heterogeneity and different thresholds for AHI or other indices limit between-study comparisons. |
| Sleepiness | For the same AHI, why are some sleepy and others not?<br>Why does sleepiness influence hemodynamic or metabolic responses to treatment or risk of recurrent events after myocardial infarction?<br>How can sleepy patients be enrolled safely into long-term randomized trials with cardiovascular end points? | Potential role for neuroplasticity of cortical arousal centers. In HFrEF with OSA, ESS scores relate inversely to MSNA. |
| Tricuspid regurgitation | Should OSA be sought and treated before intervention?<br>Does jugular venous engorgement promote upper airway collapse by increasing peripharyngeal pressure? | Clinical experience: treating OSA can cause sustained regression of severe right ventricular dilatation and tricuspid regurgitation. |

(*Continued*)

**Table 4. Continued**

| Entity | Question | Rationale |
|---|---|---|
| Ventricular arrhythmia | Should presence or absence of SDB influence the decision to implant a defibrillator for primary prevention in nonischemic cardiomyopathy? | Clinical uncertainty. Risk of appropriate discharge increased up to 2-fold if CSA or OSA present. |
| Ventricular remodeling | Is focal basal/sigmoid septal hypertrophy an echocardiographic sign of OSA with nocturnal desaturation? | Frequently identified when imaging patients with OSA. |
| Women | Why are women with OSA at less long-term risk of developing stroke, HF, or hypertension?<br>Is estrogen protective?<br>Why do so few women with HFrEF develop CSA? Does this contribute to their better overall prognosis? | Sex differences in central chemoreflex sensitivity when awake and apnea threshold with sleep. |

AHI indicates apnea–hypopnea index; BP, blood pressure; CSA, central sleep apnea; ESS, Epworth sleepiness scale; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MSNA, muscle sympathetic nerve activity; NE, norepinephrine; OSA, obstructive sleep apnea; PAP, positive airway pressure; PSG, polysomnography; and SDB, sleep-disordered breathing.

## Discussion

SDB disrupts the normal alignment of diurnal hemodynamic and autonomic rhythms with circadian variation in myocardial and vascular gene expression. The adverse pathophysiology instigated and the abundant epidemiological evidence that both OSA and CSA increase cardiometabolic risk and event rates motivated interventional studies and short-term randomized trials of SA treatment, yielding positive results. Present evidence offers particular opportunities, if OSA is treated, for improved atrial fibrillation management,[190,202,251] prevention of HFrEF, and recovery of ventricular systolic function. Nonetheless, the concept of SA as a potent modifiable risk factor has yet to enter into risk calculations concerning primordial, primary, or secondary prevention of cardiovascular disease.[252] Moreover, the sobering absence from primary or secondary prevention trials powered for cardiovascular end points, thus far, of any class I evidence to support therapeutic recommendations[253–255] more than disappoints. It challenges the entire intervention–benefit proposition for nonsleepy patients with OSA or HF patients with either OSA or CSA (Table 3).

Enthusiasts chagrined by the limitations of available evidence can advocate, justifiably, that equipoise remains as to whether these conditions should be identified and treated for reasons other than improving sleep quality and daytime sleepiness.[35,256] Skeptics will caution against the use of PAP in patients with HFrEF, and CSA and will contend that, with evidence of benefit absent in other populations, both screening for SDB in nonsleepy individuals for either primary or secondary cardiovascular prevention and investment to enhance diagnostic capacity are unwarranted. All concede that to avoid inadvertently treating CSA, polysomnographic interpretation of patients with HFrEF should be deferred to centers expert in discriminating between central and obstructive hypopneas with CSR.[251]

Why this existential impasse? Have investigators aspiring to secure definitive evidence of treatment efficacy erred by conducting instead pragmatic trials of management strategies? Mounting large randomized trials of sleep-specific interventions with rigorous polysomnographic analysis has been extraordinarily difficult both logistically because of the obligate close cooperation of expert sleep and cardiovascular investigators at each site and financially because of the resource constraints of sponsoring agencies. Importantly, as trials of efficacy, each conducted to date has been compromised by inadequacies in 1, more, or all of device technology, primary event rates, statistical power, and adherence to assigned therapy. Unlike drug therapy, where an effect may persist even when a dose is missed, SDB will resurface immediately if a patient ceases device use. A consistent observation has been post hoc evidence of cardiovascular benefit if effective PAP use extends into the latter hours of the night, when REM sleep and desaturation duration are the most profound.[253–255]

Have individuals at the greatest cardiovascular risk and thus the most likely to benefit from effective intervention been excluded from trials? Thus far, few professing EDS have been evaluated. Importantly, in SAVE, a $Pao_2$ <80% for >10% of recording time was an exclusion criterion. For HF-focused trials, a persistent bias to treat severely hypoxemic patients preemptively continues to impede recruitment, despite the absence of evidence of cardiovascular benefit. Future trials of effective therapy might yield definitive results if enriched by individuals with these characteristics. For CSA–CSR, the question may have been answered negatively, by SERVE-HF, in which individuals with the most advanced HF fared the worst; whether this trial's results were a consequence of the mv-ASV algorithm and full face mask used remains unresolved. If the focus is on primary prevention of cardiovascular events by abolishing OSA, then a younger cohort with longer follow-up—a daunting challenge—may be required.

Has the apposite index of disease severity been targeted? AHI, which has been the common currency of both clinical practice and clinical trials, relates inversely to cycle length. Thus, for OSA with an extraordinarily high AHI, the duration of apnea may be too short to permit clinically significant decreases in oxygen desaturation or intrathoracic pressure or reflex sympathetic activation. Ironically, individuals with a lower AHI but longer cycle length might be at greater cardiovascular risk. The same arithmetic function pertains to CSA–CSR, in which short cycles of hyperpnea and apnea identify individuals with relatively preserved lung–ear circulation time and cardiac output.[216] Thus, without specific knowledge of its impact on cycle length, a reduction in central apnea–hypopnea index with ineffective therapy might, paradoxically, signal depression of cardiac output. As documented by several

groups,[65,70,222] in OSA, the depth and duration of desaturation may be a more potent marker of cardiovascular risk than the AHI, whereas for CSA, desaturation,[222,223,244] the apnea–hypopnea cycle length, and its change during interventions may be more insightful than AHI with regard to disease severity and treatment potential. The frequencies of arousal[31] and periodic leg movements, which in HFrEF increase independently the risk of death,[257] also merit consideration.

Are investigators too deeply anchored to an intervention that may be best only a half-measure, adopted only half-heartedly by patients? If so, is the field now ripe for disruptive innovation? Interest and resources are now pivoting to different therapies.

For OSA, the value of lifestyle changes, such as weight reduction, exercise, and abstinence from alcohol, merit reinforcement.[258] Alternate strategies, such as drugs, and diuretics and mineralocorticoid antagonists in particular[259,260]; devices such as mandibular advancement[258] or hypoglossal nerve stimulation[261]; compression stockings by day to attenuate nocturnal rostral fluid shift[262]; oropharyngeal exercises[263]; or postural interventions[92] have been evaluated but not with respect to cardiovascular outcomes.

The challenge of achieving and then maintaining effective treatment of CSA with PAP devices has motivated tests of alternate therapeutic strategies, including aggressive diuresis, nocturnal supplementary oxygen[264]; overdrive pacing,[265,266] and transvenous phrenic nerve stimulation.[267] Modest reductions in AHI have been shown with each of these interventions, but these have not been accompanied consistently by improvement in surrogates of cardiovascular end points or freedom from procedural complications.[267] By improving hemodynamics, biventricular pacing can attenuate CSA acutely, but chronically, moderate-to-severe apnea persists in the majority of patients.[226,265] Neither overdrive pacing nor cardiac resynchronization therapy affect obstructive apnea frequency.[266] Brief, small trials of theophylline[268] or inhaled $CO_2$[269] have demonstrated efficacy but also pragmatic, safety, and tolerability issues. Carotid body ablation or denervation is also being evaluated.[270]

Rather than a failure of methods, do the present neutral results of treatment trials indicate a failure of concept? Do sleep-related breathing disorders confer, in their own way, unappreciated benefits that are offset by current modes of targeted therapy? Do the cycles of hypoxemia and reoxygenation in OSA, for example, induce cardiac and cerebral preconditioning? Is CSA an agonal compensatory response to falling cardiac output and tissue perfusion, undermined by excessive inspiratory and expiratory pressure support? The likelihood that these questions will be resolved soon by requisite large randomized trials is remote.

Nonetheless, the pathophysiology of SDB and its concurrence and interaction with other systems and disease states remain fertile ground for mechanistic research questions with potential clinical impact on defined populations. A sampling appears in Table 4. Until such uncertainty evaporates and more efficient population screening is available, SA will remain a clinically clandestine threat to homeostatic cardiovascular rhythms and an enigmatic cardiovascular risk factor.

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